A small molecule screen to identify regulators of let-7 targets.

Public Summary:

We performed a drug discovery screen targeting a gene, let-7, to find compounds that inhibit its activity. Let-7 is a regulatory gene that promotes cancer cell development and growth. After screening through roughly 36,000 compounds, we identified a class of compounds that suppress let-7 targets. As a result, these compounds also show growth inhibitory activity on cancer cells.

Scientific Abstract:

The let-7 family of miRNAs has been shown to be crucial in many aspects of biology, from the regulation of developmental timing to cancer. The available methods to regulate this family of miRNAs have so far been mostly genetic and therefore not easily performed experimentally. Here, we describe a small molecule screen designed to identify regulators of let-7 targets in human cells. In particular, we focused our efforts on the identification of small molecules that could suppress let-7 targets, as these could serve to potentially intercede in tumors driven by loss of let-7 activity. After screening through roughly 36,000 compounds, we identified a class of phosphodiesterase inhibitors that suppress let-7 targets. These compounds stimulate cAMP levels and raise mature let-7 levels to suppress let-7 target genes in multiple cancer cell lines such as HMGA2 and MYC. As a result, these compounds also show growth inhibitory activity on cancer cells.

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